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EXAMINER
WALICKA, MALGORZATA A

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1652	

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9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,982	DURDEN, DONALD L.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) 1-8 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 9-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The application is the national stage of the PCT/US00/07981 application. Claims 1-15 are pending and are the subject of this Office Action.

OFFICE ACTION

1. Restriction/Election

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I claim(s) 1-8, drawn to a method of preventing and treating an autoimmune disease that respond to asparagines or glutamine depletion by administering to a human patient therapeutically effective amount of an asparaginase or a glutaminase.

Group II claim(s) 9-15, drawn to a method of preventing or treating graft versus host disease by administering to a human patient therapeutically effective amount of an asparaginase or a glutaminase.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I-II seem to be a treatment with asparaginase or glutaminase. However, this is not a special technical feature as it is not a contribution over prior art; see review by Hersh E. et al. (Immunosuppression by

L-Asparaginase and Related Enzymes, *Transplantation*, **1971**, 12, 368-376, included in examiner's references, a copy enclosed).

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

During a telephone conversation with Applicant representative Michael Wise, on August 21, 2003, a provisional election was made without traverse to prosecute the invention of Group II, claims 9-15. Affirmation of this election must be made by Applicant in replying to this Office Action.

Claims 1-8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Priority

The application is the national stage of the PCT/US00/07981, filled on March 24, 2000 and claiming priority to the US provisional Application No. 60/127,662 filed April 2, 1999. However, the section Related Applications on page 1 of the specification claims Priority to US Patent Application Serial No. 09/094,435 filed June 9, 1998, which in turn claims priority to the US provisional Application 60/049085 filed June 9, 1997.

The oath or declaration is defective, because the oath claims priority to the PCT/US00/07981 application only. A new oath or declaration in compliance with 37 CFR 1.67(a) claiming priority to US application No. 60/127,662 filed April 2, 1999, No.

09/094,435 filed June 9, 1998, and No. 60/049085 filed June 9, 1997 is required. See MPEP §§ 602.01 and 602.02.

3. ***Rejections***

3.1.UC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim recites the phrase "wherein said glutaminase is *Acitenobacte".* The recitation is confusing, because Acitenobacter is a genus of bacterial cells and not an enzyme." The correct phrase should be "wherein said glutaminase is from *Acitenobacter."*

3.2. 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact

terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1. Written description

Claims 9-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to two genera of methods of preventing or treating graft versus host disease by administering to a human patient therapeutically effective amount of an asparaginase or a glutaminase.

The claims are directed to a large genus of method using a genus of native and man-made asparaginases and glutaminases that are not sufficiently described in the disclosure, because they enzyme used in the methods are lacking structural identification.

Although Applicants teach as sources of asparaginase two bacterial species, *E. coli (EC) and*, *Wolinella succinogens (WS),* as well as genus *Erwinia*, and as a source of glutaminase, one bacterial genus, *Actienobacter*, the structural characteristics of the enzymes is not disclosed, with exception for the asparaginase from *Wolinella*

succinogens whose amino acid sequence can be translated from its encoding gene of SEQ ID NO: 3.

In addition, those skilled in the art realize that bacterial species can have several asparaginases or glutaminases. Applicants mention, for example, two asparaginases of *E. coli*, one of which is induced by anaerobic conditions; see page 2 of the specification. Thus, mentioning the source of the enzyme cannot be a substitute for its amino acid sequence identifying its structure.

Furthermore, not any asparaginase can be used in the claimed methods, because not every asparaginase has immunosuppressive properties necessary for the methods. Applicants disclose on page 3 line 19, "In contrast, asparagine deprivation alone, caused by the administration of the glutaminase-free **asparaginase from *WS***, does not affect spleen histology or lymphocyte marker distribution and **is not immunosuppressive** [emphasis added]." Therefore, the amino acid structure of the enzyme to be used has to be disclosed as this is the structure that determines the immunosuppressive properties of the protein.

Because the disclosure lacks identifying structural characterisitics of the claimed genera of enzymes, one skilled in the relevant art is not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 10-15 are also rejected because the claims are directed to the use of asparaginase selected from the group consisting of EC, WS and *Erwinia* asparaginase,

as well as glutaminase from *Acitenobacter,* in the method of preventing or treating graft vs host disease (GVHD). The disclosure, however, teaches only, "*E.coli* asparaginase can ameliorate the severity of acute GVHD in this model [the murine bone marrow transplant model for graft vs host disease, the only model used by Applicants, MW]" (see Example 16, page 51, line 22). The specification fails to teach that *WS* asparaginase, *Erwinia* asparaginase or glutaminase from *Acitenobacter* can also ameliorate the severity of acute GVHD in this model. Furthermore, the specification is silent as to which *EC* asparaginase has the reported ameliorating effect; is this a native or inducible asparaginase or any of modifications thereof? Taking into account the lack of written description one skilled in the relevant art is not convinced that the inventor(s), at the time the application was filed, had possession of the claimed invention.

3.2.2. Scope of enablement

Claim 9-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of preventing or treating GVHD in mouse model system using *EC* asparaginase injections (3 injections of 50 IU/per injection per week, during 4 weeks), does not reasonably provide enablement for treating a human patient with any asparaginase or glutaminase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The scope of the claims is broader than the scope of the disclosure. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Otherwise, undue experimentation is necessary to make the claimed invention.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses two genera of methods of treating or preventing GVHD disease in human, wherein said methods use asparaginase or glutaminase from any natural or man-made source.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that the claimed genera of methods have effects as intended by Applicants. The provision of treatment, in the laboratory model of GVHD, by one enzyme, i.e. asparaginase for *E.coli*, does not provide sufficient guidance as to which of thousands of known and to be disclosed asparaginases and glutaminases have immunosupressant activity in human body, so that they can be used in treatment of GVHD. The

experimentation left to those skilled in the art has a low probability of success without further guidance on the part of Applicants as to the structure of the enzymes that have the proper immunosupressant activity. It is known that not every asparaginase or glutaminase has an immunosuppressive action. Applicants themselves indicate on page 3 line 19: "...asparagine deprivation alone, caused by the administration of the glutaminase-free **asparaginase** from *WS*, does not affect spleen histology or lymphocyte marker distribution and **is not immunosuppressive** [emphasis added]." **Furthermore, Applicants results presented in Example 16 suggest asparaginase from *Wolinella succinogenes* and *Erwinia* asparginase as well as glutaminase from** *Acitenobacter* do not exibit immunossupressive properties in the used mouse model of GVHD. In addition, as pointed out by Lubkowski et al. (Crystal structure and amino acid sequence of *Wolinella sucinogens* L-asparaginase, Eur. J. Biochem. 1996, 241, 201-207; see page 201 right column line 1), the problem encountered in clinical use of asparaginases is their low stability in the human circulatory system. *Wolinella sucinogens* L-asparaginase, has a lower toxicity and longer plasma half-life than asparaginase from *E. coli*; *Ibidem*, page 202, left column, line 14). However, Applicants' data do not provide evidence that the enzyme has a proper characteristics from the point of view of use in the treatment of GVHD.

Because Applicants failed to provide the guidance as to the structure of the enzymes that have the proper immunosupressant characteristics, experimentation left to those skilled in the art is improperly extensive and undue.

3.4. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action: The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levin et al. (Immunosuppressive Activity of L-Asparaginase, Transplantation, 1971, 12, 141-143), Rapaport et al. (Prolongation of Canine Renal Allograft survival by L-asparaginase, Transplantation, 1971, 12, 217-221) and further in view of Hersh E. et al. (Immunosuppression by L-Asparaginase and Related Enzymes, *Transplantation*, **1971**, 12, 368-376); copies of all publications included in examiner's references.

The claim is directed to a method of treating graft versus host disease by administering to a human patient therapeutically effective amount of an asparaginase or L- asparaginase from *E. coli,* or L- asparaginase from *E. coli* wherein said asparaginase is native or recombinant.

Levin et al. and Rapaport et al. showed that graft vs. host disease in animal models (rat and dog, respectively) can be reversed by treatment with L-asparaginase; see *Results* and *Abstracts* of both papers.

Levin et al used L-asparaginase purchesed from Lilly, from unknown organism, but most probably from *E. coli*; see page 142, left column, 17 line under Table 1 showing results of treatment.

Rapaport et al. used L-asparaginase purchased from Merck Sharpe and Dohme (page 219, right column, line 30). The L-asparaginase produced by Merck Sharpe and Dohme was *Escherichia coli* asparaginase (Ohno et al, Immunosuppressive Effects of L-Asparaginase, Cancer Research, 1970,30, 1605-1611; copy enclosed, page 1605, right column, line 24). This enzyme was native, because the recombinant production of enzymes was unknown at that time.

Hersh teaches "the effects of L-asparaginase treatment on cell-mediated immunity in man have already been described" (page 372 right column, line 33) and concludes, "These data [Levin et al. and Rapaport et al.] coupled with the observation that 3-7day courses of L-asparaginase in man are immunosuppressive *(67)* [Ohno et al.], suggest that the use of this drug [i.e. of L-asparaginase] in human transplantation be given careful consideration" (page 373, left column, line 9).

It would have been obvious to one having ordinary skill in the art at the time of invention to have L-asparaginase, and specifically L-asparaginase from *E.coli*, as taught by Levine et al. and Rapaport et al., and use it in the method of treatment of graft vs. host disease in human as suggested by Hersh.

It would be also obvious to use a native or recombinatly produced enzyme, because the native asparaginase has been in use for more than 30 years, and recombinant production of enzymes is routine since at least 20 years.

The expectation of success has been high taking into account positive results in the animal models.

The motivation has been also provided by Hersh, who concluded, "It seems possible the addition of a 1-3-week course of this drug in the immediate postgraft period would significantly improve graft survival", page 373, right column, the last line.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

4. Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

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